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TITLE OF THE INVENTION (500 characters max)

Methods For Preventing Deterioration In Mass and/or Increasing Mass In Lymphatic Organs

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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ENCLOSED APPLICATION PARTS *(check all that apply)*

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Respectfully submitted,

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Date January 13, 2004

REGISTRATION NO. 47,545 *(if appropriate)*

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Provisional Patent Application
Docket No. OBI-103P

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Docket No. : OBI-103P

Applicant(s) : Kwan Po Wong and Francis Chi

For : Methods For Preventing Deterioration In Mass and/or Increasing Mass In Lymphatic Organs

Mail Stop Provisional Patent Application
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DESCRIPTION

METHODS FOR PREVENTING DETERIORATION IN MASS AND/OR INCREASING MASS IN LYMPHATIC ORGANS

Background of the Invention

The immune system is a highly complex, biological system that requires the cooperation of a large number of different cell types. The systems of the body that make up the immune system network are variously categorized as belonging to the hematopoietic system, the reticuloendothelial or phagocytic system, and the lymphatic system.

The lymphatic system is made up of lymphocytes, and is responsible for the overall regulation of the immune system and for the production of antibodies. Lymphocytes can be concentrated within organs or can form a more or less diffuse lymphoid tissue, both of which collectively constitute the lymphatic system. Primary lymphatic organs (also known as "central tissues"), such as the thymus and bone marrow, are the major sites of lymphopoiesis. Secondary lymphoid organs and tissues (also known as "peripheral tissues"), such as the spleen, lymph nodes, lymphoid formations associated with the mucosae (or "MALT" for mucosal associated lymphoid tissue), Peyer's patches, and palatine tonsils, are those sites within which lymphocytes can interact with one another or with a foreign substance or organism (also known as an "antigen"). In addition, a large number of lymphocytes can be found in the mucosa of the stomach, of the small intestine, of the colon, of the bronchi and of various other organs.

Although there are many classes of lymphocytes, T-lymphocytes (or T-cells) and B-lymphocytes (or B-cells) make up a majority of the lymphocyte population. B-lymphocytes are generally responsible for the production of antibodies (immunoglobulin) in response to a challenge by a particular antigen. T-lymphocytes are responsible for the general regulation of the immune system and are also the principal mediators in cell-mediated immune responses.

All lymphocytes are ultimately derived from stem cells in bone marrow. These lymphocyte precursors are dispersed into the blood where they course through many organs. However, critical events take place in the thymus that imprint the lymphocytes with special functions and that regulate lymphocyte development into either T- or B-lymphocytes.

B-lymphocytes have significantly different biological functions from those of T-lymphocytes. While B-lymphocytes are involved in the final pathway of the humoral immune system (antibody production), T-lymphocytes encompass several subtypes of cells that play roles varying from immune system regulation to execution of the cytotoxic immune system. In addition to being responsible for antibody production, B-cells have some ability to engulf and "present" the antigen to a specific T-cell (also known as a T-helper cell) to stimulate the immune system.

T-lymphocytes are formed in the thymus from lymphoblasts that have left the bone marrow. The thymic cortex is rich in lymphocytes of all sizes. These thymocytes are not morphologically distinguishable from lymphocytes in other tissues, but they are immature and antigenically identifiable by the presence of several cell surface antigens including the T antigen, which is a distinctive surface marker antigen that separates the T-lymphocyte from the B-lymphocyte.

T-lymphocytes are actually divided into several subsets and the role that they play in the immune system is complex. The T-lymphocyte is responsible for two important immunological phenomenon: the cell-mediated immune response and the humoral immune response. In a cell-mediated immune response, the T-lymphocytes that recognize a cell-bound antigen begin producing and secreting a wide variety of proteins that affect the activity of other types of cells in the immune system. These proteins include lymphokines that attract, activate and hold phagocytes at the site of the antigen and interferons that provide protection against virus infection.

In the humoral immune response, the T-lymphocyte is an important regulator of B-lymphocyte function. The antigen-exposed T-lymphocyte may have either of two direct and opposite effects on B-lymphocytes depending on the subclass of T-lymphocyte. The major subclasses are the helper cell and the other is the suppressor cell.

Helper T-lymphocytes are necessary for a complete B-cell response to T-lymphocyte dependent antigens. T-lymphocyte dependent antigens tend to be the more complex antigens such as bacterial proteins, virus proteins and other large complex proteins in general.

Anatomically, the thymus is situated in the anterior thoracic cage over the heart. A bilobed organ, the thymus is composed of epithelial cells and other structural cells that divide it into a complex assembly of continuous lobes, each of which is heavily laden with lymphocytes. The thymus is nourished and drained by the vascular and lymphatic systems, and innervated by the autonomic nerves.

Embryologically, the thymus emerges from the third and fourth branchial pouches. The human thymus is a fully developed organ at birth and weights 15 to 20 grams. By puberty it weighs 40 grams, after which it atrophies or involutes becoming less significant structurally and functionally. Atrophy of the thymus with age is a characteristic of all species, which is associated with aging, and the cessation of growth. The incidence of age related diseases increases as the thymus shrinks and thymus-dependent immunity decreases. This age-associated decrease in thymic weight, called "involution," is accompanied by changes in the thymic structure and a general decline in thymic function.

Thus, the thymus is normally active only during the early years of life. During those years, the thymus supplies T-lymphocytes that will serve the animal for the rest of its life. In certain diseases, such as rheumatoid arthritis, the thymus may regain some activity during adult life. This demonstrates that the adult thymus retains capacity to function and that involution is not necessarily permanent. At least partial function might be restored if the appropriate agents were available.

Transient involution of the thymus may also occur as a consequence of a stress or infection. Thymic involution may be controlled hormonally; castration slows involution while injection of corticosteroid hormones accelerates involution. Numerous studies have demonstrated that the thymic involution associated with increasing age parallels a reduction of T-lymphocyte-mediated immunity and increased incidence of diseases

associated with aging. Many diseases and treatments can accelerate involution of the thymus; virtually none are known to enhance growth of the thymus or reverse involution.

The spleen serves at least four major physiologic functions. First, as part of the peripheral immune system, it clears the blood of microorganisms and particulate antigens and/or generates antigens to foreign substances. Second, it sequesters and removes excess, old and/or abnormal blood cells. Third, its vasculature is involved in the regulation of portal blood flow. Finally, it engages in hematopoiesis during development or when the bone marrow alone cannot produce sufficient blood cells.

The spleen, which is located under the left side of the diaphragm, receives blood from an artery off of the aorta. Nests of B-lymphocytes surround the blood vessels of the spleen. After passing through this intricate meshwork of tiny blood vessels, the blood continues to the liver.

The spleen consists of red pulp, which contains blood-filled sinuses and pulp cords lined by reticuloendothelial cells, and of white pulp, which is arranged around a central arteriole. The surrounding periarteriolar lymphoid sheath (PALS) contains both T- and B-lymphocyte areas. The T-lymphocyte area lies adjacent to the arteriole and consists of small, densely packed lymphocytes. Outside of the T-cell area is the follicular zone, which contains B-lymphocytes, and germinal centers, which are made up of B-cells and macrophages. The white pulp is surrounded by a marginal zone containing specialized, antigen-presenting macrophages and B-cells.

In the spleen as well as other tissues, leukocytes including monocytes, macrophages, basophils, and eosinophils play important roles in the pathological mechanisms initiated by T- and/or B-lymphocytes. Macrophages, in particular, produce powerful oxidants and proteases, which contribute to tissue destruction and secrete a range of cytokines, which recruit and activate other inflammatory cells.

The intestine is the organ richest in lymphocyte cells, which circulate in blood vessels and lymph vessels, or which collect and multiply in the small intestine (major lymphocytic tissues in the small intestine known as Peyer's patches). These lymphoctyic cells are a component of MALT, which is subdivided into gut-associated lymphoid tissues ("GALT") situated in the intestine and into bronchial-associated lymphoid tissues

("BALT") situated in the bronchi, and which has analogies with skin-associated lymphoid tissues ("SALT") situated in the skin. GALT and BALT are interdependent and act in synergism to ensure the immune defense of the mucosa and to contribute towards the defense of the organism as a whole.

Unlike the lymph node, the Peyer's patches (PP) does not have a capsule of afferent lymphatics. The epithelium over the PP lacks the crypts and villi of normal gut epithelium and is referred to as follicle-associated epithelium (FAE) containing cells called M cells. These are the major route of antigen transfer into the PP, and allow for direct sampling of antigen from the gut lumen by pinocytosis. Antigen is transported from the epithelium and presented to immunocompetent B-cells, macrophages and dendritic cells in the underlying area. The colon has similar lymphoid arrangements called the lymphoid follicles. Lymphoid follicles are not identical to PP, but also have specialized epithelium containing M cells, and probably function as antigen presenting sites.

Underneath the epithelium there is a tissue called the lamina propria, which forms the core of the villus and is densely infiltrated with lymphocytes bearing homing receptors, which selectively bind to the mucosal lymphoid high endothelium. B-cells comprise about 50% of the lymphocytes in the lamina propria of the gut, whereas the other half of lymphocytes are T-cells. In the normal intestine, most of the B-cells in the lamina propria are IgA+, although IgM-, IgG- and IgD-expressing cells are also found. Most of the immunoglobulin secreted into the intestine is IgA, and half of that is IgA-2, in contrast to the lymph nodes where most of the secreted IgA is of the IgA-1 isotype. The abundance of IgA antibodies is considered crucial for immunological homeostasis within the lamina propria. IgA antibodies lack potent effector functions such as complement activation, and may therefore block non-specific biological amplification mechanisms triggered by locally produced or serum-derived IgG antibodies.

As already mentioned, T-cells classified as T-helper cells comprise approximately half of the lymphocytes in the lamina propria. This phenotype is generally prevalent in human PP, and specifically in the interfollicular zones surrounding the high endothelial

venules (HEV). In contrast, T-lymphocytes classified as T-suppressor (or CD8+) are predominant in the epithelium of humans.

Although it is not clear how inductive and suppressive immunoregulatory mechanisms are achieved in the gut, the lamina propria and epithelium, along with the organized lymphoepithelial nodules and the larger lymphoid aggregates, *e.g.* PP, are probably all involved in a complex manner.

AIDS is a disease caused by the human T-lymphocyte lymphotrophic virus (formerly LAV or HTLV-III; currently designated HIV). The virus specifically attacks T-helper lymphocytes, a subgroup of T-lymphocytes that plays a major role in defending the body against infectious diseases. Depletion of this subset of lymphocytes is manifested by an increased incidence of opportunistic infections like pneumocystis carinii and certain cancers. More specifically, the virus enters the T-lymphocyte and incorporates viral encoded DNA into the DNA of the host T-lymphocyte. As long as the infected T-lymphocyte remains inactivated, the virus will quietly remain in the DNA of the host cell. This will not kill the cell but may impair its function.

When the infected T-lymphocytes are activated by stimuli such as a specific antigen, the viral DNA in the host DNA is expressed and produces new viral particles. The host T-lymphocyte is then killed and lysed, releasing new viral particles that can invade and kill other T-lymphocytes. The loss of T-helper lymphocytes is profound and occurs even faster than can be accounted for by direct viral killing of the cells. This has led some investigators to postulate that the infection somehow shuts off the production of T-helper lymphocytes.

Studies have demonstrated that the thymus in the normal adult is slowly involuting and is no longer functioning. Moreover, in the normal adult, killed T-lymphocytes cannot be replaced, thus leaving the patient vulnerable to subsequent infectious. Especially striking are recent studies of the thymuses of deceased AIDS patients ranging in age from 10 months to 42 years. AIDS victims have profound thymic involution; much more extensive than in age-matched patients who died of other causes.

It has been postulated that to cure a person with AIDS will require one agent to eliminate the virus and other agents to cause the body to replace T cells that have been

killed by the virus. The first step is to eliminate the AIDS virus from the patient. This will have to be supported by other therapies to induce restoration of immune function. Studies to date with macrophage activating agents, interferon inducers and lymphokines have been disappointing, possibly because their targets, T-lymphocytes, do not exist in sufficient numbers. Interleukin-2 (also known as IL-2) restores the function of one subset of non T-cells (natural killer cells) but has no effect on a host of other serious defects. More drastic measures can be performed. One potential method of restoring the immune system is by transplanting bone marrow from healthy donors. However, this is a dangerous procedure. It may produce lethal graft versus host disease unless the patient's donor is an identical twin.

Another area where there is a need to re-establish the lymphatic system, and also the hematopoietic system, is in total body irradiation for treatment of leukemia. When a patient undergoes high dose total body irradiation, the entire immune system is compromised. The usual treatment after the irradiation is to perform a bone marrow transplant with marrow from a close relative. If the transplant is successful, the new marrow will produce new cells, thereby restoring both red blood cells and white blood cells to the body. However, this is a dangerous treatment that is successful in only a fraction of the cases. Localized radiation of tumors and several types of chemotherapy also produce suppression of T-cell mediated immunity.

Current methods of immunization by systemic administration have not demonstrated good efficacy in protecting against the establishment of a pathogen in the mucosae. It is desirable, if not essential, to induce an immunization by mucosal administration, possibly in addition to an immunization by systemic administration, in order to combat this type of infection with efficacy. Immunization by mucosal administration makes it possible in essence to stimulate the lymphoid tissue draining the mucosa(e) where the pathogen is lodged, and thus to obtain an immune response targeted at the mucosa(e).

Therefore, what is needed is a safe and effective method of stimulating immune responsiveness (*i.e.*, by restoring or enhancing T- and B-lymphocyte function) in the lympathic system, in particular to stimulate growth in the thymus and spleen. Further,

there is needed a means for enhancing villi length and goblet cell production in mucosae. In doing so, non-specific immune response is augmented.

One method is by treating existing T- and B-lymphocytes so that they resume their normal immune functions. Agents that have been shown to be effective in certain situations in stimulating T- and/or B-lymphocytes include macrophate activating factors, interferon inducing agents, lymphokines, and cytokines. However, in a disease such as AIDS or in the case of irradiation in which the T- and/or B-lymphocyte population has been destroyed, this type of treatment is not effective because the number of T- or B-lymphocytes is severely depleted. In these cases, an effective method of causing the thymus to produce new T-lymphocytes and of causing the spleen to increase hematopoiesis activity would be the treatment of choice. However, to date, there is no effective treatment that will cause the thymus to reverse the process of involution and produce new T-lymphocytes. Nor has a successful method been provided to enhance splenic function and/or enhance mucosa protection against pathogens.

Brief Summary of the Invention

The subject invention provides methods for affecting biological immune systems in many different ways. In particular, the biologically active cysteamine compound of the present invention is capable of stimulating an increase in mass (or retarding the deterioration in mass) in the thymus and/or the spleen. Further, administration of a cysteamine compound of the present invention to a patient can enhance the ability of mucosa to combat and/or prevent the occurrence of immunological diseases/disorders. In doing so, the subject invention provides effective methods for enhancing immunological responsiveness.

The biologically-active cysteamine compound of the present invention can be administered orally, or by other known routes of administration such as via parenteral, intravenous, intramuscular, transdermal, buccal, subcutaneous, or suppository administration.

In one embodiment, a cysteamine compound is administered to a patient to restore, maintain, and/or improve the performance of a patient's lymphatic system. By

providing a cysteamine compound, the patient's immune system is augmented due to biological responses in various lymphatic organs/tissues. For example, after the administration of a cysteamine compound, the patient's thymus and/or spleen maintain their mass and/or increase in mass; which enhances both T- and B-cell bioactivity. Moreover, cysteamine compounds enable increased growth in villi along mucosal linings and increased goblet cell activity to enhance non-specific immune defenses against antigens.

In another embodiment of the invention, a cysteamine compound is administered to a patient diagnosed with an immunological disorder and/or condition to treat the disorder/condition as well as prevent and/or decrease the severity of complications related to the disorder/condition. In a related embodiment, a cysteamine compound is administered in combination with other known agents that are used to treat immunological disorders/conditions (*i.e.*, autoimmune, inflammatory, proliferative and hyperproliferative diseases, cutaneous manifestations of immunologically mediated diseases).

Specifically exemplified herein is the use of a cysteamine compound to increase or maintain the mass of the thymus and/or spleen. Further, in a related embodiment, the use of a cysteamine compound increases villi length and goblet cell production in mucosa(e) in a patient to enhance immunological responsiveness. For example, common immunological disorders and/or conditions such as autoimmune disorders (*i.e.*, Hashimoto's thyroiditis, pernidcious anemia, Addison's disease, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, Sjogren's syndrome, dermatomyositis, lupus erthematosus, multiple sclerosis, myasthenia gravis, Reiter's syndrome, Graves disease), immune deficiency (*i.e.*, AIDS), and multiple chemical sensitivity, can be treated through administration, according to the subject invention, of a cysteamine compound.

Accordingly, an object of the present invention is to provide a method for stimulating maintenance and/or growth in thymus and/or spleen mass; or stimulating mucosae bioactivity in a patient, preferably an adult patient.

In accordance with the subject invention, administration of a cysteamine compound to a patient can alter the patient's immune system to either ameliorate, treat, and/or prevent the occurrence of an immunological disease/disorder that would develop in the absence of cysteamine.

Brief Description of Drawings

Figure 1 shows a metabolic pathway of cysteamine.

Figure 2 shows cysteamine as a constituent of co-enzyme A.

Detailed Disclosure of the Invention

The subject invention provides methods for treating patients diagnosed with immunological diseases/disorders or preventing the occurrence of such diseases/disorders in a patient. In preferred embodiments, the invention provides methods for maintaining and/or preventing the deterioration in mass of thymus and/or spleen in patient. In other embodiments, the present invention provides methods for affecting mucosae bioactivity, namely increasing villi growth and goblet cell activity, in order to treat and/or prevent the development of immunological diseases/disorders.

As used herein, "immunological diseases/disorders" includes conditions associated with previous treatment with chemotherapeutic agents, radiation, immunosuppressive and anti-inflammatory drugs and dialysis; conditions such as severe combined immunodeficiency, congenital thymic aplasia, aplastic anemia, viral infections, chronic granulomatous disease and immune dysfunction associated with diabetes; adverse reactions to bone marrow or organ transplantation such as graft-versus-host disease; physical findings such as rashes, fevers, and adverse reactions indicative of leukemias, lymphomas, inflammatory bowel disease or psoriasis. In addition, the term "immunological diseases/disorders" includes diseases classified as autoimmune in nature (see, Theofilopoulos, A., In: D. P. Stites, *et al.*, eds., Basic and Clinical Immunology, Lange Medical Publications, Los Altos, Calif., 1988, which is incorporated in its entirety by reference).

In certain embodiments, methods of the present invention are used for retarding the deterioration of and/or maintaining mass in the thymus and/or spleen of a patient to treat and/or prevent the development of immunological diseases/disorders including immune mediated cancers and hyperactive immune responses. Such immune mediated cancers may include lymphoreticular neoplasia, lymphoblastic leukemia, brain tumors, gastric tumors, plasmacytomas, multiple myeloma, leukemia, connective tissue tumors, solid tumors and lymphomas. Such hyperactive immune responses may include asthma/allergies and autoimmune diseases. Such allergies may include hay fever, atopic dermatitis, urticaria, perennial rhinitis, allergic conjunctivitis, pulmonary diseases, food allergies, skin allergies, anaphylaxis (*e.g.*, associated upon exposure to blood products) and pollinosis.

In other embodiments, methods of the present invention are used for preventing the deterioration of and/or maintaining the mass in the thymus and/or spleen of a patient to treat and/or prevent the development of autoimmune diseases including, without limitation, type 1 diabetes, conventional organ specific autoimmunity, neurological disease, rheumatic diseases/connective tissue disease, autoimmune cytopenias, and related autoimmune diseases. Conventional organ specific autoimmunity may include thyroiditis (Graves+Hashimoto's), gastritis, adrenalitis (Addison's), ovaritis, primary biliary cirrhosis, myasthenia gravis, gonadal failure, hypoparathyroidism, alopecia, malabsorption syndrome, pernicious anemia, hepatitis, anti-receptor antibody diseases and vitiligo. Neurological diseases may include schizophrenia, Alzheimer's disease, depression, hypopituitarism, diabetes insipidus, sicca syndrome and multiple sclerosis. Such rheumatic diseases/connective tissue diseases may include rheumatoid arthritis, systemic lupus erythematous (SLE) or Lupus, scleroderma, polymyositis, inflammatory bowel disease, dermatomyositis, ulcerative colitis, Crohn's disease, vasculitis, psoriatic arthritis, exfoliative psoriatic dermatitis, pemphigus vulgaris, Sjorgren's syndrome. Other autoimmune related diseases may include autoimmune uvoretinitis, glomerulonephritis, post, myocardial infarction cardiotomy syndrome, pulmonary hemosiderosis, amyloidosis, sarcoidosis, aphthous stomatitis, and other immune related diseases, as presented herein and known in the related arts. See, *e.g.*, Berkow *et al.*, eds, The Merck

Manual, 16th edition, Merck and Co., Rahway, N.J., 1992, pages 303-364, 710-718, 1083, 1269, 1305-1377, 1338 1677-1684, and 2435-2438 which is incorporated herein in its entirety by reference.

The term "patient," as used herein, describes an organism, including mammals, to which treatment with the compositions according to the present invention is provided. Mammalian species that benefit from the disclosed methods of treatment include, and are not limited to, apes, chimpanzees, orangutans, humans, monkeys; and domesticated animals (*i.e.*, pets) such as dogs, cats, mice, rats, guinea pigs, and hamsters.

As used herein, reference to a "cysteamine compound" includes the various cysteamine salts (such as cysteamine hydrochloride and cysteamine phosphate) as well as prodrugs of cysteamine that can, for example, be readily metabolized in the body to produce cysteamine. Various analogs, derivatives, conjugates, and metabolites of cysteamine are well known and readily used by those skilled in the art and include, for example, compounds, compositions and methods of delivery as set forth in U.S. Patent Nos. 6,521,266; 6,468,522; and 5,714,519.

The term "effective amount," as used herein, refers to the amount necessary to elicit the desired biological response. In accordance with the subject invention, the effective amount of cysteamine is the amount necessary to decrease a particular sign and/or symptom (*i.e.*, increase or drop in body temperature, level of IgE, *etc.*) of an immunological disease/disorder. The decrease may be a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 98% or 99% decrease.

Specifically exemplified herein is the use of cysteamine hydrochloride (and/or analogs, derivatives and prodrugs thereof) to treat and/or prevent the occurrence of an immunological disease/disorder in a patient.

In one embodiment of the subject invention, the advantages of cysteamine, as set forth herein, can be achieved by promoting the endogenous production of cysteamine through natural metabolic process such as through the action of co-enzyme A or as a metabolite of cysteine (see Figures 1 and 2). This can be achieved by, for example, the administration of pantethenic acid.

One method to increase levels of cysteamine involves pantothenic acid. Pantothenic acid is a naturally occurring vitamin that is converted in mammals to coenzyme A, a substance vital to many physiological reactions. Cysteamine is a component of coenzyme A, and increasing coenzyme A levels results in increased levels of circulating cysteamine. Alkali metal salts, such as magnesium phosphate tribasic and magnesium sulphite (Epsom salts), enhance formation of coenzyme A. Furthermore, breakdown of coenzyme A to cysteamine is enhanced by the presence of a reducing agent, such as citric acid. Thus, the combination of pantothenic acid and alkali metal salts results in increased coenzyme A production and, concomitantly, cysteamine.

Administration of the cysteamine, in accordance with the subject invention, can be accomplished by any suitable method and technique presently or prospectively known to those skilled in the art. In a preferred embodiment, the cysteamine compound is formulated in a patentable and easily consumed oral formulation such as a pill, lozenge, tablet, gum, beverage, *etc.* The consumption is then taken at, shortly before, or after, the time of introduction to an antigen.

Compositions comprising cysteamine can be formulated according to known methods for preparing pharmaceutically useful compositions. Formulations are described in detail in a number of sources that are well known and readily available to those skilled in the art. For example, *Remington's Pharmaceutical Science* by E.W. Martin describes formulations, which can be used in connection with the subject invention. In general, the compositions of the subject invention will be formulated such that an effective amount of the bioactive compound(s) is combined with a suitable carrier in order to facilitate effective administration of the composition.

In accordance with the invention, compositions comprising, as an active ingredient, an effective amount of the cysteamine and one or more non-toxic, pharmaceutically acceptable carrier or diluent. Examples of such carriers for use in the invention include ethanol, dimethyl sulfoxide, glycerol, silica, alumina, starch, and equivalent carriers and diluents.

To provide for the administration of such dosages for the desired therapeutic treatment, compositions of the invention will typically comprise between about 0.1% and

45%, of the total composition including carrier or diluent. The dosage used can be varied based upon the age, weight, health, or the gender of the individual to be treated.

In one embodiment, the dosage of cysteamine administered to a patient to elicit a desired response is substantially 50 mg or greater. In a preferred embodiment, the dosage of cysteamine administered to a patient to elicit a desired response depends on the physiological characteristics of the patient, with dosage amounts of 50, 75, 100, 125, 150, 175, 200, 225, 250, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650, 675, 700, 725, 750, 775, 800 mg. More preferably, the dosage of cysteamine administered to a patient to elicit a desired response is about 200-500mg.

The compositions of the invention can be used in a variety of forms, *i.e.*, tablets, capsules, pills, powders, aerosols, granules, and oral solutions or suspensions and the like containing the indicated suitable quantities of the active ingredient. Such compositions are referred to herein generically as "pharmaceutical compositions." Typically, they can be in unit dosage form, namely, in physically discrete units suitable as unitary dosages for human consumption, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with one or more pharmaceutically acceptable other ingredients, *i.e.*, diluent or carrier.

Following are examples that illustrate procedures for practicing the invention. These examples should not be construed as limiting. All percentages are by weight and all solvent mixture proportions are by volume unless otherwise noted.

Example 1—Administration of Cysteamine Compound and Immune Response in Murine Model

Male C57BL/6N mice were used in the experiment, 28 in total. 28 mice were used for pretest for 7 days before the treatment began. Two groups of 14 mice were created. As illustrated in Table 1, 12 mice from group 1 was orally administered a cysteamine compound, 27% (w/w) cysteamine hydrochloride, at a dosage of 40 mg/kg or 80 mg/kg of body weight. Each group contained six replicates and each replicate contained 8 mice. The treatment period was for 30 days.

Table 1—Experimental Model

Control	Saline
Treatment 1	Cysteamine hydrochloride-40mg/kg BW
Treatment 2	Cysteamine hydrochloride-80mg/kg BW

Lymphocytes transformation rate in plasma, white blood cell (WBC) count, natural killer cell activity, Plasma IL-2 (Kit provided by Jingmei Biotech) and IL-6 (Kit provided by Bender MedSystems) measurement, and antibody forming cell count were performed according to methods known to the skilled artisan. (See "Medical Immunology Experiment," Publisher: People Hygiene, Published in 1999 in China, Editor: Xi Chuan Ping). Five days before the end of the treatment, 12 mice from each group (each replicate for 2 mice) were immunized with 0.5 ml of 2% sheep RBC (equivalent to $2x10^8$ cells per ml) for testing spleen B-cells. The relative weights of spleen and thymus to body weight (mg/ 100g BW) were also measured. All statistical analyses were performed on ANOVA.

After conducting all tests and analyses, the relative weight of certain immune organs, namely the thymus and spleen, were measured, as illustrated in Table 2.

Table 2—Measurement of Organ Weight (mg/100g of body weight)

Organ	Control	Treatment 1	Treatment 2
Thymus	534±5.04^{C}	549±1.89^{B}	567±7.18^{A}
Spleen	290±6.33	298±5.03	296±7.50

Note: Different superscript means statistically significant difference
"A" and "B" or "B" and "C" means $P<0.05$
"A" and "C" means $P<0.01$

The WBC count, lymphocyte transformation rate (specifically in the spleen), antibody forming cell, and natural killer cell killing rate (based on the killing rate of K562 cells by natural killer cell) were measured and analyzed, as illustrated in Tables 3 and 4.

Table 3—Analyses of Treatments

Item	Control	Treatment 1	Treatment 2
WBC Count (10^9/L)	6.78±0.54	7.12±0.65	7.53±0.55
Lymphocytes Transformation (SI Value, SI means Stimulation Index)	1.10±0.05^{B}	1.15±0.02^{B}	1.24±0.05^{A}
Antibody Forming Cell (OD, Optical Density)	1.44±0.23^{A}	1.48±0.19^{A}	0.91±0.51^{C}
NK Killing Rate (%)	90.29±2.24	92.19±2.20	93.60±2.21

Table 4—Plasma IL-2 and IL-6 Measurements

Item	Control	Treatment 1	Treatment 2
IL-2 (pg/ml)	6.05±0.44	5.88±0.53	5.76±0.50
IL-6 (pg/ml)	247.83±49.40	226.20±37.93	247.00±51.76

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Lymphocyte transformation (or SI Value) is provided using CPM (Count per minute) of PHA containing tube / CPM (Count per minute) of tube without PHA. PHA-Phytohemagglutinin can stimulate inactive T-cell to convert to parental cell, which will eventually convert to active T-cell. In this regards, the stimulating index reflects the amount of inactivate T-cell available for turning into active T-cell. Thus, with a higher index, more inactive T-cells are present.

All patents, patent applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application.

Claims

I claim:

1. A method for retarding the deterioration in mass of thymus in a patient wherein said method comprises administering, to the patient an effective amount of a cysteamine compound.

2. The method, according to claim 1, wherein said cysteamine compound is selected from the group consisting of cysteamine, cysteamine salts, prodrugs of cysteamine, analogs of cysteamine, derivatives of cysteamine, conjugates of cysteamine, and metabolites of cysteamine.

3. The method, according to claim 2, wherein said cysteamine salt is cysteamine hydrochloride or cysteamine phosphate.

4. The method, according to claim 1, wherein said cysteamine compound is taken orally, parenterally, intravenously, intramuscularly, transdermally, via buccal route, subcutaneously, or via suppository.

5. A method for maintaining mass of thymus in a patient wherein said method comprises administering, to the patient an effective amount of a cysteamine compound.

6. The method, according to claim 5, wherein said cysteamine compound is selected from the group consisting of cysteamine, cysteamine salts, prodrugs of cysteamine, analogs of cysteamine, derivatives of cysteamine, conjugates of cysteamine, and metabolites of cysteamine.

7. The method, according to claim 6, wherein said cysteamine salt is cysteamine hydrochloride or cysteamine phosphate.

8. The method, according to claim 5, wherein said cysteamine compound is taken orally, parenterally, intravenously, intramuscularly, transdermally, via buccal route, subcutaneously, or via suppository.

9. A method for maintaining mass of spleen in a patient wherein said method comprises administering, to the patient an effective amount of a cysteamine compound.

10. The method, according to claim 9, wherein said cysteamine compound is selected from the group consisting of cysteamine, cysteamine salts, prodrugs of cysteamine, analogs of cysteamine, derivatives of cysteamine, conjugates of cysteamine, and metabolites of cysteamine.

11. The method, according to claim 10, wherein said cysteamine salt is cysteamine hydrochloride or cysteamine phosphate.

12. The method, according to claim 9, wherein said cysteamine compound is taken orally, parenterally, intravenously, intramuscularly, transdermally, via buccal route, subcutaneously, or via suppository.

13. A method for increasing growth in villi along mucosal linings in a patient wherein said method comprises administering, to the patient an effective amount of a cysteamine compound.

14. The method, according to claim 13, wherein said cysteamine compound is selected from the group consisting of cysteamine, cysteamine salts, prodrugs of cysteamine, analogs of cysteamine, derivatives of cysteamine, conjugates of cysteamine, and metabolites of cysteamine.

15. The method, according to claim 14, wherein said cysteamine salt is cysteamine hydrochloride or cysteamine phosphate.

16. The method, according to claim 13, wherein said cysteamine compound is taken orally, parenterally, intravenously, intramuscularly, transdermally, via buccal route, subcutaneously, or via suppository.

17. A method for increasing goblet cell activity in a patient wherein said method comprises administering, to the patient an effective amount of a cysteamine compound.

18. The method, according to claim 17, wherein said cysteamine compound is selected from the group consisting of cysteamine, cysteamine salts, prodrugs of cysteamine, analogs of cysteamine, derivatives of cysteamine, conjugates of cysteamine, and metabolites of cysteamine.

19. The method, according to claim 18, wherein said cysteamine salt is cysteamine hydrochloride or cysteamine phosphate.

20. The method, according to claim 17, wherein said cysteamine compound is taken orally, parenterally, intravenously, intramuscularly, transdermally, via buccal route, subcutaneously, or via suppository.

Abstract

The present invention relates to materials and methods useful in augmenting immune response. In particular, the present invention provides biologically-active compounds that can cause the thymus and spleen to increase in size and cause an increase in villi length and goblet cell production in mucosae. Specifically exemplified herein is the use of a cysteamine compound to modulate immune responsiveness. In a preferred embodiment, oral administration of cysteamine hydrochloride to a patient retards the deterioration in mass and/or maintains mass in thymus and spleen, and enhances mucosae bioactivity to bolster patient immunity.

Cysteamine – Constituent of Co-enzyme A

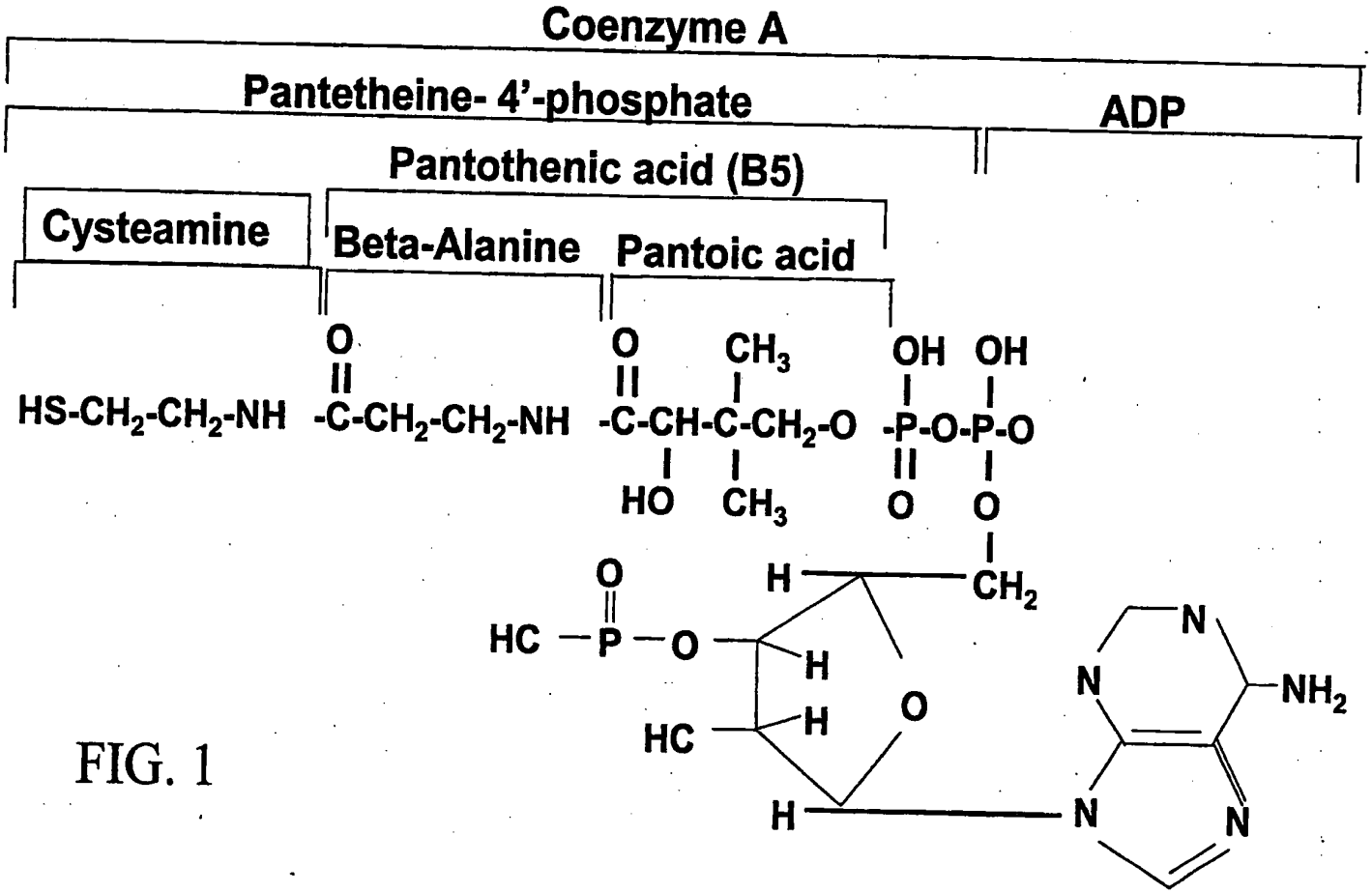

FIG. 1

Metabolic Pathway of Cysteamine

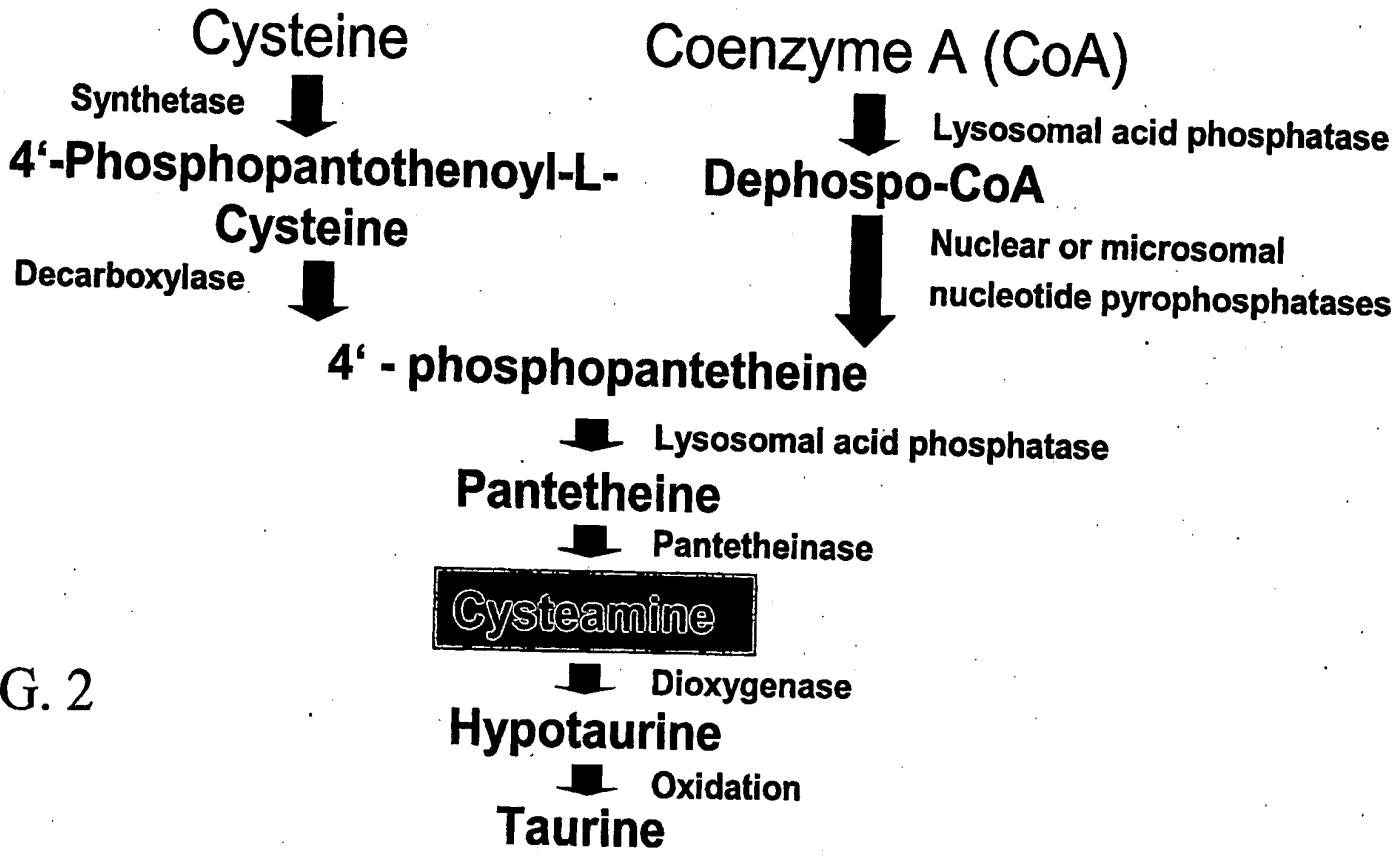

FIG. 2